## REMARKS

Reconsideration of the present application in view of the following remarks is respectfully requested. Claims 1-17 are pending in the application. Claims 4-17 have been withdrawn from consideration. Support for the amendment to claim 1 can be found throughout the specification, but particularly in Example 1 on pages 17-18 and in Table 6 on page 19. Claims 1-3 are currently under examination. No new matter has been added by way of this amendment.

### *Claim Rejection under 35 U.S.C. §103*

Claims 1-3 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Johnson *et al.* (Journal of Virology, Apr. 1998, Vol. 72, No. 4, pages 2871-2880) in view of Firestone *et al.* (Virology, 1996. Vol. 225, pages 419-422. Article No. 0618, Short Communication).

The invention, as currently claimed, is directed to a method of identifying an attenuated respiratory syncytial virus (RSV) strain that produces high yields of RSV **surface glycoprotein F** when compared to parent strain A2. The method comprises: providing a eukaryotic cell culture, infecting the cell culture with a live, attenuated RSV; and **determining the glycoprotein F concentration, wherein at least a five-fold increase in glycoprotein F concentration is an indication that the attenuated strain produces high yields of RSV F glycoprotein compared with the parent A2 strain**, wherein the RSV mutant strain is cpts-2481404, wherein the eukaryotic cells are VERO, MRC-5, FRhl, GEF or PER.C6 cell culture.

The Examiner's Position

The Examiner alleges that Johnson *et al.* (hereinafter Johnson) teaches the G glycoprotein has been implicated as an RSV antigen that promotes activation of the Th2 CD4+ T-lymphocyte and induces eosinophilic infiltrates in the lung following RSV challenge (page 287 1, 1st column, 1st paragraph). Johnson teaches the large glycoprotein G serves as the attachment protein of RSV and is one of the major glycoproteins expressed in the membrane of the virus. The protein is expressed on the surface of the infected cell and secreted into the extracellular environment (page 2871,

I[st] column. 2[nd] paragraph). Johnson also teaches a method of purifying and measuring the secreted RSV G protein from RSV A2 strain (page 2872, 1[st] column, 3[rd] paragraph and page 2873, I[st] column, 1[st] paragraph). Johnson does not teach an attenuated RSV, mutant strain cpks-248/404 or using VERO cells.

The Examiner alleges that Firestone *et al.* (hereinafter Firestone) teaches a live attenuated RSV strain, cpt-248/404 mutant, differs from its wild-type RSV strain A2 by increased G when passaged in VERO cell culture (Abstract and page 420, 2[nd] column). Firestone teaches attenuating RSV and the comparison of wild-type RSV A2 grown in HEp-2 cells, cold-passages cp-RSV, and temperature-sensitive cpts-248 (Abstract and page 2872, I[st] column, 2"d paragraph). Firestone teaches how the cpts-248/404 mutant differs from its wild-type RSV A2/HEK7 parent (Abstract). Firestone also teaches the predominant nucleotide in cpts-248/404 is G and that this can be used for identification of the cpts-248/404 mutant (pages 421-422, joining paragraph).

The Examiner alleges that it would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to identify a high glycoprotein producing RSV. The Examiner alleges that a person of ordinary skill in the art would have been motivated because Johnson teaches the importance of the glycoprotein and how to measure the glycoprotein, and Firestone teaches a comparison of attenuated RSVs to the wild-type RSV, and as such, one reasonably would have expected success because of the teachings of Johnson and Firestone.

Applicants respectfully submit that the Examiner has failed to set forth a *prima facie* case of obviousness because the references cited by the examiner, when viewed as a whole, neither teach nor suggest all the claim limitations. In particular, the references do not teach or suggest a method as claimed for identifying an attenuated respiratory syncytial virus (RSV) strain that produces high yields of RSV surface glycoprotein F when compared to parent strain A2. Moreover, Applicants assert that the references do not teach or suggest that the strain so identified by the methods described in the present invention is *cpts*-248/404, which may be grown in eukaryotic cells selected from VERO, MRC-5, FRhL, CEF or PER.C6 cell culture.

Applicants respectfully traverse the stated grounds for rejection and submit that the combination of Johnson and Firestone, viewed as a whole, neither teaches nor suggests the subject matter of instant claims 1-3.

Johnson

Johnson teaches the use of vaccinia virus vectors that express either wild type G glycoprotein, or soluble/secreted G glycoprotein, or membrane bound G glycoprotein for determining the effect of G priming on immunopathogenesis.

As noted by the Examiner, Johnson does not teach an attenuated RSV, in particular, *cpts*-248/404, or using VERO cells. Also, Johnson **does not teach or suggest a method of identifying an attenuated respiratory syncytial virus (RSV) strain that produces high yields of RSV surface glycoprotein F, as currently claimed,** when compared to the parent A2 strain.

More particularly, Johnson does not teach or suggest a method of identifying an RSV strain that produces high yields of RSV surface **glycoprotein F**, wherein the strain so identified is the RSV mutant strain *cpts*-248/404.

Furthermore, Johnson does not teach or suggest a method of identifying an RSV strain that produces high yields of RSV surface **glycoprotein F**, wherein the strain is grown in VERO cells, MRC-5 cells, FRhL cells, CEF cells or PER.C6 cells.

Firestone

Firestone teaches the nucleic acid sequence of the RSV mutant strain cpts-248/404. More particularly, the studies conducted by Firestone were done in an attempt to determine which nucleotides played a role in temperature sensitivity and/or attenuation. Applicants respectfully point out to the Examiner that Applicants could not find any reference to an increase in levels of glycoprotein G by this mutant strain in the abstract, or on page 420, column 2. It is Applicants' belief that the Examiner mistook the reference to "G" in this paper to mean the "G" glycoprotein, whereas the authors were in fact referring to the "G" nucleotide, as the sequence analysis was of primary importance to dissect the role of particular nucleotides in temperature sensitivity and/or attenuation.

Firestone **does not teach or suggest a method of identifying an attenuated respiratory syncytial virus (RSV) strain that produces high yields of RSV surface glycoprotein F, as currently claimed,** when compared to the parent A2 strain.

More particularly, Firestone does not teach or suggest a method of identifying an RSV strain that produces high yields of RSV surface **glycoprotein F**, wherein the strain so identified is the RSV mutant strain *cpts*-248/404.

Furthermore, Firestone does not teach or suggest a method of identifying an RSV strain that produces high yields of RSV surface **glycoprotein F**, wherein the strain is grown in VERO cells, MRC-5 cells, FRhL cells, CEF cells or PER.C6 cells.

The Analysis under 35 USC 103(a)

To establish a *prima facie* case of obviousness, three criteria must be met. First, the prior art references, when combined, must teach or suggest all the claim limitations. Second, there must be a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine the teachings within the references. Third, there must be a reasonable expectation of success in achieving the claimed invention. See MPEP § 2143.

Accordingly, a finding of obviousness under § 103 requires a determination of the scope and content of the prior art, the differences between the claimed invention and the prior art, the level of ordinary skill in the art, and whether the differences are such that the claimed subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Graham v. Deere, 383 US 1 (1966). Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion that the combination be made. In re Stencel, 828 F2d 751, 4 USPQ2d 1071 (Fed. Cir. 1987).

The arguments advanced by the Examiner fail to meet all of these criteria for the current invention, as presently claimed. More particularly, any rejection based on Johnson and Firestone, alone or in combination, fails for at least the following reasons.

1. There simply is no teaching or suggestion in the references, alone or in combination, for **a method of identifying an attenuated respiratory syncytial virus (RSV) strain that produces high yields of RSV surface glycoprotein F, as currently claimed,** when compared to the parent A2 strain using the methods of the present invention, whereby at least a five-fold increase in **glycoprotein F** concentration is an indication that the attenuated strain produces high yields of **RSV F glycoprotein.**

2. There simply is no teaching or suggestion in the references, alone or in combination, for a method of identifying an RSV strain that produces high yields of RSV

surface **glycoprotein F**, wherein the strain so identified is the RSV mutant strain *cpts*-248/404.

3. There simply is no teaching or suggestion in the references, alone or in combination, for a method of identifying an RSV strain that produces high yields of RSV surface **glycoprotein F**, wherein the strain is grown in VERO cells, MRC-5 cells, FRhL cells, CEF cells or PER.C6 cells.

4. Taking the references as a whole, Applicants assert that there is no motivation, either in the reference(s) themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the teachings found in the cited references to achieve Applicants' claimed invention. Furthermore, Applicants assert that the outcome observed through use of the methods of the invention were not known, and could not be predicted based on the cited references, given the fact that neither of the references cited teach or suggest the use of the methods of the invention to identify strains of RSV that demonstrate production of increased yield of glycoprotein F of the RSV mutant described herein. It was only at the time of the present invention that it was determined that strain *cpts*-248/404, while showing a 1000 fold restriction in replication compared to wild type virus, and a 100 fold restriction in replication to the parent A2 strain at 37° C, could in fact show an unexpected five fold increase in production of the F glycoprotein at 30° C.

In sum, the references cited by the Examiner do not teach or suggest the subject matter provided by amended claim 1. Furthermore, neither of the references cited by the Examiner, or the knowledge generally available to one of ordinary skill in the art, would have provided any motivation to combine the teachings of Johnson in view of Firestone in order to achieve the presently claimed invention. More specifically, the references cited by the Examiner would not have suggested to one of skill in the art that a *cpts*-248/404 mutant, which replicates poorly in cells at 37°C, could produce a five fold increase in the F glycoprotein at 30°C, thus making it a highly desirable candidate for vaccine production. In fact, one might predict completely opposite results to those observed with this *cpts*-248/404 attenuated strain, that is, a decrease in production of

the F glycoprotein, not an increase, given the fact that this strain is restricted in replication compared to the wild type or parent strain.

Applicants therefore submit that claim 1 is not obvious over Johnson in view of Firestone. Each of claims 2-3 depend from the subject matter of claim 1. Thus, the patentability of each of claims 2-3 under 35 U.S.C. § 103(a) necessarily follows from the non-obviousness of claim 1. Applicants respectfully request that the rejection of claims 1-3 be withdrawn.

***Conclusion***

It is submitted that the claims are in condition for allowance, and an early and favorable action on the merits is requested. No new matter has been introduced by way of this amendment. In the event that there are any questions concerning this amendment, or the application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,

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